REMARKS

As an initial remark, Applicants thank the Examiner for explaining, during a telephonic interview conducted on November 29, 2005, that the PTO-326 form mistakenly indicated a two-month period for reply to the present Office Action; the Examiner noted that the correct period for reply is the standard three-month period.

Claims 55-57, 59-68, 72-77, and 79-100 are currently pending. Claims 87 and 97 have been amended to correct a misspelled word; other amendments are discussed below. Consideration of the amendments and the remarks herein is respectfully requested.

Rejection of the claims under 35 U.S.C. §112, 2nd paragraph

At page 14 of the Office Action, the Examiner has rejected claims 90-96 and 98-100 as indefinite because the phrase "the phenotypic change" at the end of claims 90-96 and 98 allegedly lacks antecedent basis. As suggested by the Examiner, Applicants have replaced this phrase with "degradation of Type II collagen in joints" to parallel the language found in the preamble of the claims. For this reason, Applicants respectfully request withdrawal of this indefiniteness-based rejection of claims 90-96 and 98-100.

In one instance, the Examiner appears to maintain a previous indefiniteness-based rejection of claim 97. (Office Action, dated November 7, 2005, at page 14, first line). However, neither this Office Action, nor the previous Office Action (dated November 2, 2004) clarify why claim 97 is rejected as indefinite, and therefore Applicants believe this rejection is in error.

Rejection of claims under 35 U.S.C. §112, 1st paragraph

I. Written Description-Based Rejections

The Examiner has rejected claims 55-57, 59-64, 66-68, 72-77, 79 and 81-100 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter that lacks an adequate written description. Specifically, on page 3 of the instant Office Action, the Examiner asserts that the phrase "chondrocyte-specific promoter" as recited in the claims is not adequately described because the specification allegedly does not disclose any promoters that meet the Examiner's definition of "chondrocyte-specific promoter" other than the type II collagen promoter. The Examiner maintains on page 4 of the instant Office Action that "[g]iven the teachings in the specification, the limitation of 'chondrocyte-specific promoter' is limited to the definition of 'joint-specific expression' on page 15, line 19-20, i.e. expression that is greater in chondrocytes than in other tissues; typically, the level of expression in non-joint tissues is less than 10%."[1] The Examiner maintains that the specification describes only one structure, i.e., the type II collagen promoter, having the function of a "joint-specific promoter" as defined by the Examiner, and that "[d]escribing the structure of one species within a genus defined by function is not adequate written description of other structures within the genus." (Office Action, dated November 7, 2005, at p. 4). For the following reasons, that rejection is respectfully traversed.

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[1]/This assertion by the Examiner is at odds with the Office Action, dated April 9, 2003, in which the Examiner asserts that the phrases "joint-specific promoter" and "chondrocyte-specific promoter" could not be used interchangeably. (See, Office Action, dated April 9, 2003, at p. 4, wherein the Examiner states that "the Type II collagen promoter is a 'joint-specific promoter' not a 'chondrocyte-specific promoter' as claimed."). In fact, in that Office Action, dated April 9, 2003, the Examiner explicitly stated on page 4 that the description of "joint-specific expression" provided on page 15 of the application - the description now relied on by the Examiner to define "chondrocyte-specific expression"- does not define promoters specific to chondrocytes.

A specification need not provide *ipsis verbis* support for a claim limitation. *Martin v. Johnson*, 454 F.2d 746, 751 (C.C.P.A. 1972). MPEP §2163 states that "there is no *in haec verba* requirement" for compliance with the written description standard; rather "newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure." MPEP 8th Ed., Rev. 2 (May 2004), p. 2100-167. Thus, the fact that the phrase "chondrocyte-specific promoter" is not expressly defined in the instant specification does not render the claims invalid under 35 U.S.C. §112 as long as Applicants reasonably convey to one skilled in the art that they possessed the subject matter of the claims at the time the application was filed. *See, e.g., Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991). Applicants respectfully submit that they have reasonably conveyed to one skilled in the art that they possessed transgenic rats, comprised of, *inter alia*, a repressor-activator fusion polypeptide or a transcription activator protein operatively linked to a chondrocyte-specific promoter.

Interpretation of "Chondrocyte-Specific Promoter"

During examination, a pending claim must be given the broadest reasonable interpretation consistent with the specification. *In re Hyatt*, 211 F.3d 1367, 1372 (Fed. Cir. 2000). Unless an applicant has provided a clear definition in the specification, claim terms and phrases must be given their plain meaning. *In re Zletz*, 893 F.2d 319, 321 (Fed. Cir. 1989). When interpreting the plain meaning of a term or phrase in a claim, "the words are presumed to take on the ordinary and customary meanings attributed to them by those of ordinary skill in the art." *Brookhill-Wilk 1, LLC v. Intuitive Surgical, Inc.*, 334 F.3d 1294, 1298 (Fed. Cir. 2003). In the previous Response, dated September 2, 2005, Applicants amended the claims to replace the

phrase "joint-specific promoter" with the phrase "chondrocyte-specific promoter."[2] Because Applicants removed "joint-specific promoter" from the claims, it is improper to import the alleged definition of "joint-specific promoter" into the claims to limit a different phrase, i.e., "chondrocyte-specific promoter." See, *In re Prater*, 415 F.2d 1393, 1404-05 (C.C.P.A. 1969) (stating that one may not read limitations from the specification into the claims if there is no express basis in the claims for such limitation). Applicants respectfully submit that "chondrocyte-specific promoter" should be interpreted independently of "joint-specific promoter,"[3] and that, interpreted broadly, a "chondrocyte-specific promoter" refers to a promoter sequence which ensures, e.g., that "genes are selectively expressed in articular chondrocytes of the transgenic animal." (Specification, page 6, lines 4-5). Applicants also submit that the phrase "chondrocyte-specific promoter," given the ordinary and customary meaning attributed to the phrase by one skilled in the art, merely refers to a promoter that enriches expression of a particular gene in chondrocytes.

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[2]/In the previous Response, Applicants indicated that support for the new phrase "chondrocyte-specific promoter" could be found in pending claims 28, 39, 41, and 42 (filed as a Preliminary Amendment on September 20, 2000) and on page 37, line 1; page 6, lines 4-5; and page 13, lines 3-4 of the specification. (Response to Advisory Action, dated September 2, 2005 at page 19, lines 12-16). In that Response, Applicants did not state that the phrase "joint-specific promoter" is interchangeable with "chondrocyte-specific promoter," nor did Applicants cite the alleged definition identified by the Examiner on page 15, line 19 through page 16, line 2 of the specification as providing support for amending the claims to recite "chondrocyte-specific promoter."

[3]/See, e.g., page 13, lines 3-4 of the instant specification, stating "[p]referably MMP activity is selectively expressed in joint tissues, most preferably in articular chondrocytes." This statement clearly indicates that Applicants do not consider joint expression to be precisely interchangeable with chondrocyte expression.

A. The Description of "Chondrocyte-Specific Promoter" in the Specification

The phrase "chondrocyte-specific promoter" refers to a promoter sequence that allows selective expression of a particular gene in chondrocytes. (Specification, page 6, lines 4-5). The specification also makes clear that Applicants equate "selective" expression with "specific" expression. (See, e.g., Specification at page 6, lines 18-20, stating that "[s]elective expression ... results in regulated joint-specific expression"; page 15, lines 20-21, stating "joint-specific expression ... refers to expression that is greater in joints than in other cells"; and original claim 1, which claims a transgenic mammal whose "recombinant gene is selectively expressed in chondrocytes."). Thus, a chondrocyte-specific promoter is merely a selective promoter that expresses a particular gene at a higher level in chondrocytes than in other cells. In an Office Action, dated April 9, 2003, the Examiner states at page 4, line 11 that "selectively expressing in chondrocytes is not limited to specific expression."[4] Therefore, as Applicants equate "specific" expression with "selective" expression in the specification, and the Examiner believes that selective expression is not restricted to chondrocytes, the Office appears to agree

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[4]Presumably, the Examiner takes issue with the term "specific" rather than the terms "promoter" and "chondrocyte." In a previous Office Action, dated April 9, 2003, the Examiner attempted to differentiate "specific" from "selective" (see Office Action dated April 9, 2003, at page 4, lines 7-9). The Examiner provides the following definitions:

- Specific - "constituting or falling into a specifiable category ... restricted to a particular individual situation, relation or effect ..."; and
- Selectively - "*highly specific* in activity or effect." (Id., emphasis added).

As "selectively" is defined as being "*highly specific*," (i.e., more specific), it would appear that, at least in this iteration of the Examiner's definitions, "specific" can only be less restricted than "selectively." Yet, the Examiner concludes in this same Office Action that "chondrocyte-specific expression is limited to expression in chondrocytes while selectively expressing in chondrocytes is not limited to specific expression and merely requires 'highly specific' expression in chondrocytes." (Office Action, dated April 9, 2003 at page 4, lines 10-12). Regardless of Applicants confusion as to the definitions provided by the Examiner, Applicants nevertheless use "specific" interchangeably with "selective" in the specification, and use both terms to refer to a promoter that enriches expression of a gene in chondrocytes.

with Applicants that "chondrocyte-specific" promoters may drive expression of a particular gene in cells other than chondrocytes.

Assuming, *arguendo*, that the alleged definition of "joint-specific promoter" has some place in defining "chondrocyte-specific promoter," the broadest reasonable interpretation available from the alleged definition identified by the Examiner on page 15, line 19 through page 16, line 2 (see Office Action, dated November 7, 2005, at pages 3-4), is a promoter that provides "expression that is greater in joints than in other cells." The Examiner has not used the broadest reasonable interpretation from the description given for "joint-specific expression" on page 15, line 19 through page 16, line 2. The sentences identified by the Examiner read as follows:

> Spatial control of MDE expression is achieved by the use of transcriptional promoters that direct transcription selectively in joint tissues. Joint-specific expression as used herein refers to expression that is greater in joints than in other cells; *typically*, the level of expression in non-joint tissues is less than 10% of the level of expression in joints. *Preferably,* expression in non-joint tissues is undetectable. Useful promoter sequences that confer joint-specific expression on a sequence to which they are operably linked include without limitation sequences derived from the collagen type II promoter.

(Specification, page 15, line 19 through page 16, line 2 - emphasis added). This section provides a broad description for "joint-specific expression;" namely, it includes "expression that is greater in joints than in other cells." Applicants follow the broad description with a narrower description: "*typically*, the level of expression in non-joint tissues is less than 10% of the level of expression in joints;" and further provide the narrowest description: "*[p]referably,* expression in non-joint tissues is undetectable." Thus, the broadest reasonable interpretation that one could extrapolate to "chondrocyte-specific promoter" from the interpretation of "joint-specific promoter" that the Examiner derives from the description of "joint-specific expression," is a promoter that provides expression that is greater in chondrocytes than in other cells. However,

one need not resort to an extrapolated interpretation of a phrase that Applicants have removed from the claims, because the specification provides the correct description, e.g., a chondrocyte-specific promoter provides for the selective expression of genes in chondrocytes. (See specification, page 6, lines 4-5). Thus, Applicants respectfully submit that the Examiner's conclusion that "chondrocyte-specific promoter" means a promoter that "provides expression in chondrocytes while providing less than 10% expression in non-chondrocytes" (Office Action, page 6), is not the broadest reasonable interpretation of this phrase.

Additional evidence that the Examiner's definition of "chondrocyte-specific promoter" is incorrect is provided in the same paragraph identified by the Examiner. That is, Applicants state at page 15, line 23 through page 16, line 2 that useful promoter sequences "include without limitation" sequences derived from the collagen type II promoter. As a result, Applicants clearly have not limited themselves to the type II collagen promoter (as the Examiner contends), and therefore the Examiner's interpretation cannot be considered the broadest reasonable interpretation of the phrase "chondrocyte-specific promoter."

B. The Ordinary Meaning of "Chondrocyte-Specific Promoter" to One Skilled in the Art

The ordinary meaning of the phrase "chondrocyte-specific promoter" as used in the claims is further illuminated by the ordinary meaning provided in the art. Numerous publications describe genes that are enriched in chondrocytes as "chondrocyte-specific," and the expression of these genes is inherently driven by chondrocyte-specific promoters. Support for the fact that the phrase "chondrocyte-specific" indicates enriched expression in chondrocytes, rather than strict expression in chondrocytes (as the Examiner contends), may be found in the Second Declaration of Dr. Roger Askew (hereinafter "the Second Askew Declaration"), submitted herewith. Dr. Askew discusses the use of the phrase "chondrocyte-specific" as meaning a gene

that is enriched within chondrocytes (the Second Askew Declaration at point 10), and provides a summary of several scientific publications that use the phrase "chondrocyte-specific" in this manner. (Id. at point 12). For example, Dr. Askew states that Zhou et al. ((1995) J. Cell. Sci. 108:3677-84) describe Type II collagen as a "chondrocyte-specific" gene even though it is also expressed in tissues such as heart, eye and brain. (The Second Askew Declaration at point 12a). Dr. Askew states that Bosserhoff et al. ((1997) Dev. Dyn. 208:516-25)[5] describe the *CD-RAP* gene as being chondrocyte-specific. (The Second Askew Declaration at point 12b). Dr. Askew also states that Goldring et al. ((1994) J. Clin. Invest. 94:2307-16) describe collagens type IX and type XI, and Aggrecan as "chondrocyte-specific." (The Second Askew Declaration at point 12c). Dr. Askew also indicates that McDougall et al. ((1996) J. Bone Min. Res. 11:1130-38) describe the Link protein as "chondrocyte-specific," while Bosnakovski et al. ((2006 Feb. 9) Biotechnol. Bioeng. [Epub ahead of print]) describe *sox9*, *collagen type II*, *aggrecan*, and *cartilage oligomeric matrix protein* (*COMP*) as "chondrocyte-specific" genes. (The Second Askew Declaration at points 12d and 12e).

Dr. Askew further states that in addition to fitting within the art-accepted meaning for "chondrocyte-specific," the mouse *CD-RAP* promoter also fits within the definition the Examiner alleges should be applied to "chondrocyte-specific," i.e., expression that is less than 10% in non-joint tissues. (The Second Askew Declaration at points 16-17). The *CD-RAP* promoter is also extensively discussed in The Third Declaration of Dr. Lisa A. Neuhold

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[5/] Bosserhoff et al. is one of the two scientific articles referred to in the Second Declaration of Dr. Lisa A. Neuhold as part of the memo attached at Tab 2. The memo attached at Tab 2 cites the two references: Bosserhoff et al. (*supra*) and Dietz and Sandell (1996) J. Biol. Chem. 271:3311-16. It does not appear that the Examiner has reviewed these references; they are herewith provided for the Examiner's review as part of an Information Disclosure Statement, and are discussed more extensively in the Third Declaration of Dr. Lisa A. Neuhold, submitted herewith.

(hereinafter "the Third Neuhold Declaration"), submitted herewith. Dr. Neuhold states that the mouse *CD-RAP* promoter is a chondrocyte-specific promoter. (The Third Neuhold Declaration at point 9). Dr. Neuhold also reviews several articles that discuss *CD-RAP* expression and promoter activity. (Id. at points 10 and 11). Dr. Neuhold notes that Bosserhoff et al. describe *CD-RAP* as a "gene specific to chondrogenesis." (Id. at point 10). Dr Neuhold also notes that Bosserhoff et al. state that *CD-RAP* is expressed solely in the cartilage of the embryonic mouse, and is expressed solely in the cartilage of live 3-day-old mice. (Id.).

Dr. Neuhold indicates that the promoter for the chondrocyte-specific mouse *CD-RAP* gene was isolated and known in the art prior to filing the '450 application (the Third Neuhold Declaration at point 11), and that the *CD-RAP* promoter would be useful to produce a transgenic rat according to the pending claims. (Id. at point 12; see also, the Second Declaration of Dr. Lisa A. Neuhold, at p. 4, lines 1-4). In the Third Neuhold Declaration, Dr. Neuhold states that one skilled in the art would immediately recognize that the *CD-RAP* promoter is a chondrocyte-specific promoter (Id. at points 9-10), and would similarly recognize that the *CD-RAP* promoter would be useful to make a transgenic rat according to the pending claims. (Id. at points 9 and 12). Further, Dr. Neuhold states at point 14 of her declaration that, given the disclosure of Bosserhoff et al. and Dietz and Sandel, one skilled in the art would conclude that the CD-RAP promoter falls within the definition the Examiner alleges applies to "chondrocyte-specific promoter," i.e., a promoter that has less than 10% activity in non-joint tissues. (Id. at point 14).

In light of the statements in the relevant art and the statements provided in the Second Askew Declaration and the Third Neuhold Declaration, Applicants submit that many genes with chondrocyte-specific expression, which are driven by chondrocyte-specific promoters,

are well known in the art, and that the phrase "chondrocyte-specific promoter" would immediately be understood by one of ordinary skill in the art to mean a promoter that enriches the expression of a particular gene in chondrocytes.

Applicants respectfully submit that they have described the well-known genus of "chondrocyte-specific promoters" by: 1) indicating in the specification that these promoters selectively drive transcription in chondrocytes (specification, page 6, lines 4-5); 2) by providing an exemplary species within this genus, i.e., the type II collagen promoter; and, 3) by showing that the phrase "chondrocyte-specific promoter" is understood by one of skill in the art to mean a promoter that enriches expression of a gene in chondroctyes (see, e.g., the Second Askew Declaration and the publications recited therein). Because an applicant "need not teach, and preferably omits, what is well known in the art," Applicants are not required to list additional well-known species within the "chondrocyte-specific promoter" genus. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986). The Examiner has suggested at pages 4-5 of the Office Action that other chondrocyte-specific promoters "may not exist," and therefore Applicants' use of the phrase is merely a wish to identify such promoters. However, as described above, numerous genes are well known as "chondrocyte-specific," and these genes are necessarily driven by chondrocyte-specific promoters. Thus, Applicants have not presented a mere wish to identify such promoters; these promoters do exist and have been isolated (see also, the Enablement section below).

The Examiner has also stated at page 4-5 of the Office Action that Applicants have described the genus of "chondrocyte-specific promoters" by function, i.e., the ability of the promoter to drive gene expression in chondrocytes, and that a functional description fails to satisfy the written description requirement. However, a functional definition of a genus that

indicates the existence of species within the genus is an acceptable mode of satisfying the written description requirement if a skilled artisan would have understood that the inventors possessed the invention at the time of filing. *See Noelle v. Lederman*, 355 F.3d 1344, 1349-50 (Fed. Cir. 2004) (stating that an applicant may claim a genus of antibodies based on their function, i.e., their ability to bind a defined antigen). As Applicants present a representative example of a chondrocyte-specific promoter, i.e., the type II collagen promoter, and show that one skilled in the art would immediately recognize other chondrocyte-specific promoters, e.g., promoters inherently driving chondrocyte-specific genes including *CD-RAP, aggrecan, collagen type IX, link*, etc., one skilled in the art would understand that Applicants possessed a transgenic rat comprised of, *inter alia*, a chondroctye-specific promoter.

C. Applicants Have Previously Submitted At Least One Declaration Demonstrating That "Chondrocyte-Specific Promoters" Were Well Known In The Art At The Time Of Filing

The Examiner states at pages 6-8 of the instant Office Action that two declaration previously submitted by Applicants, i.e, the Declaration of Dr. Roger Askew ("the first Askew Declaration"; originally filed during prosecution of this application on September 2, 2005) and the Second Declaration of Lisa A. Neuhold, Ph.D. ("the Second Neuhold Declaration"; originally filed during prosecution of the parent 08/994,689 application on August 31, 2000, and filed during the prosecution of the instant application on April 30, 2002 as Exhibit 5), are insufficient to overcome the written description rejection of the claims. Specifically, the Examiner maintains that the papers referred to in the Askew Declaration (i.e., Pirok et al. (1997) J. Biol. Chem. 272:11566-74 (of record) and Lefebvre et al. (1998) EMBO J. 17:5718-33 (of record)) fail to describe "chondrocyte-specific promoters" that fall within the alleged definition identified by the Examiner (i.e., "joint-specific expression" discussed on page 15, lines 19-23 of the

specification). Further, the Examiner maintains at page 7, line 24 through page 8, line 2 of the instant Office Action that the Second Neuhold Declaration "does not discuss how the CD-RAP/MIA promoter meets the functional definition of a 'joint-specific promoter' provided in the specification (the level of expression in non-joint tissues is less than 10%)."

For the reasons stated above, Applicants respectfully submit that the broadest reasonable interpretation of "chondrocyte-specific promoter" is a promoter that provides preferential or selective expression of a particular gene in chondrocytes. Moreover, as Applicants explain above, even if the discussion at page 15 of the instant specification regarding "joint-specific expression" has some relevance in defining the claim limitation "chondrocyte-specific promoter," the Examiner has not applied the broadest definition given for "joint-specific expression," i.e., "expression that is greater in joints than in other cells" (specification, at page 15, line 21). Applicants submit that if the Examiner applies the correct interpretation of "chondrocyte-specific promoter," then at least the Second Neuhold Declaration provides facts supporting the contention that "chondrocyte-specific promoters" are currently well known, and were well known in the art at the time of filing.

Dr. Neuhold states at page 4 of the Second Neuhold Declaration that the type II collagen promoter is "by no means essential" and that "[o]ther chondrocyte-specific promoters can be substituted for it." (Second Neuhold Declaration at page 4, lines 1-4). In fact, Dr. Neuhold states that "the CD-RAP/MIA gene promoter is one such substitute for the type II collagen promoter." (Id.). In discussing "chondrocyte-specific promoters," and more specifically the *CD-RAP* promoter, Dr. Neuhold refers to the memo attached at Tab 2. (Second Neuhold Declaration at page 4, line 3). The memo attached at Tab 2 states that CD-RAP "is expressed throughout chondrogenesis and is co-expressed with type II collagen" and cites two references, Bosserhoff et

al., *supra* and Dietz and Sandell, *supra* to support these facts. Bosserhoff et al. state that "[t]he availability of a gene specific to chondrogenesis [*CD-RAP*] and co-expressed with type IIB procollagen provides a template for study of *chondrocyte-specific* gene expression" (Bosserhoff et al. at p. 520, column 1, emphasis added). Thus, Bosserhoff et al. describe *CD-RAP* as a "chondrocyte-specific" gene. (See id.). Moreover, Bosserhoff et al. note that *CD-RAP* is even more specific to cartilage than type II collagen, because *CD-RAP* is not expressed in many tissues that type IIA procollagen is located, e.g., somites, notochord, etc. (Bosserhoff et al. at page 520, column 1). As the Examiner states at page 6, lines 3-5 of the instant Office Action that the type II collagen promoter is a "chondrocyte-specific promoter," the *CD-RAP* promoter must also be a "chondrocyte-specific promoter."

The Second Neuhold Declaration also cites Dietz and Sandell, *supra* in the memo attached at Tab 2. (Second Neuhold Declaration at page 4, line 3). Deitz and Sandell report at page 3315 of their article that *CD-RAP* was only found in "the cartilaginous tissues, but from none of the other tissues that were tested."[6] Moreover, the running title of the Deitz and Sandell research article is "A *Chondrocyte-specific* mRNA" (emphasis added) (Deitz and Sandell, running title atop pages 3312-16). Thus, Deitz and Sandell also characterize *CD-RAP* as a gene with a "chondrocyte-specific" promoter. It does not appear that the Examiner has reviewed these references cited in the Second Neuhold Declaration (Tab 2) to support Dr. Neuhold's assertion that chondrocyte-specific promoters, including the type II collagen promoter and the CD-RAP promoter, were known to exist at the time of filing (Second Neuhold Declaration, paragraph 8).

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[6]This fits the Examiner's current definition of "chondrocyte-specific promoter" (based on the "joint-specific expression" passage) wherein the promoter provides "less than 10% expression in non-chondrocytes." (Office Action, dated November 7, 2005 at page 7, lines 19-21).

Thus, for the Examiner's consideration, Applicants provide herewith: 1) the Third Neuhold Declaration (described extensively above), which discusses *CD-RAP* and the relevance of the *CD-RAP* promoter to the pending claims; and 2) Bosserhoff et al. and Deitz and Sandell, which are cited in the Second and Third Neuhold Declarations.

For the reasons set forth above, Applicants believe that they have fully described "chondrocyte-specific promoters" and that the written description-based rejections of claims 55-57, 59-64, 66-68, 72-77, 79 and 81-100 have been fully answered and successfully overcome. For this reason, Applicants respectfully request withdrawal of these rejections of claims 55-57, 59-64, 66-68, 72-77, 79 and 81-100.

II. Enablement-Based Rejections

The Examiner has also rejected claims 55-57, 59-64, 66-68, 72-77, 79 and 81-100 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter that is not enabled. While the Examiner states on page 6, lines 3-5 of the instant Office Action that the type II collagen promoter is a "chondrocyte-specific promoter[]," the Examiner asserts that Applicants have not described other promoters falling within the alleged definition of "joint-specific promoter" (based on "joint-specific expression") located at page 15, lines 19-23 of the specification. Specifically, on page 10 of the Office Action, the Examiner alleges that the specification only enables a transgenic rat or mouse whose genome comprises, *inter alia*, a nucleotide sequence encoding a transcription activator or repressor protein operatively linked to a type II collagen promoter, and does not enable one to make and use the invention commensurate with the scope of the claims due to the phrase "chondrocyte-specific promoter." For the following reasons, that rejection is respectfully traversed.

The Examiner maintains that the limitation "chondrocyte-specific promoter" is limited to the definition of "joint-specific expression" on page 15, line 20 through page 16, line 2. More specifically, the Examiner maintains on page 13 that a "chondrocyte-specific promoter" is "limited to those [promoters] that cause less than 10% expression in non-chondrocytes... ." For the reasons set forth in the previous section (Written Description Section), Applicants respectfully submit that the Examiner's interpretation of "chondrocyte-specific promoter" is not the broadest reasonable interpretation of this phrase.[7] A "chondrocyte-specific promoter" is merely a promoter that selectively directs expression of a given gene in chondrocytes. (Specification, page 6, lines 4-5). In addition, Applicants have provided extensive evidence in the previous section that the phrase "chondrocyte-specific" is commonly used in the art to refer to those genes that are enriched in chondrocytes (e.g., *collagen types II, IX,* and *XI, aggrecan, CD-RAP, link, sox9,* and *COMP*). These genes are inherently driven by chondrocyte-specific promoters, many of which (e.g., *collagen types II, IX,* and *XI, aggrecan, CD-RAP, COMP, sox9,* and *link*) were isolated and characterized well before the Applicants filed the instant application. As evidence that numerous chondrocyte-specific promoters have been previously isolated, Dr. Askew discusses such promoters in the Second Askew Declaration, and indicates that many of these chondrocyte-specific promoters were isolated prior to filing the instant application (the Second Askew Declaration at point 13). The papers discussing such chondrocyte-specific promoters (the Second Askew Declaration at points 13-15), which characterize various mouse

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[7]/MPEP 2164.04 states that "[b]efore any analysis of enablement can occur, it is necessary for the examiner to construe the claims. For terms that are not well-known in the art, or for terms that could have more than one meaning, it is necessary that the examiner select the definition that he/she intends to use when examining the application." Therefore, it is not appropriate for the Examiner to assign a definition to a claim element unless the Examiner has first determined if there is an art specific meaning for the phrase "chondrocyte-specific."

and rat promoters from genes defined in the art as "chondrocyte-specific" (id. at point 12), are provided herewith.[8] Dr. Askew states that these promoters would be useful to produce a transgenic rat according to the pending claims, and that one skilled in the art would immediately recognize that these "chondrocyte-specific" promoters could be used to produce a transgenic rat according to the pending claims. (Id. at point 14). Therefore, while the "working examples are limited to the type II collagen promoter" as stated by the Examiner on page 12 of the Office Action, many other "chondrocyte-specific promoters" are and were well known in the art. As numerous promoters that are "chondrocyte-specific" are known to exist, Applicants are not required to list these promoters in order to provide an enabling disclosure. *See Hybritech*, 802 F.2d at 1384 (Fed. Cir. 1986).

The Examiner has the burden of showing "a reasonable basis to question the enablement provided for the claimed invention," and only then must Applicant "present persuasive arguments...that one skilled in the art would be able to make and use the claimed invention." (MPEP §2164.05). The Examiner alleges that no amount of experimentation would ensure that chondrocyte-specific promoters existed. (Office Action, dated November 7, 2005 at p.12). However, the Examiner has not provided any facts or reasonable basis to suggest that

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[8]/The promoters referred to by Dr. Askew at points 13 and 15 of the Second Askew Declaration are: Doege et al. (1994) J. Biol. Chem. 269:29232-40 (characterizing the rat *aggrecan* promoter); Watanabe et al. (1995) Biochem. J. 308:433-40 (characterizing the mouse *aggrecan* promoter); Xie et al. (1998) J. Biol. Chem. 273:5026-32 and Xie et al. (2000) Matrix Biology 19:501-09 (characterizing the mouse *CD-RAP* promoter); Perala et al. (1994) J. Biol. Chem. 269:5064-71 (characterizing the mouse *collagen type IX* promoter); Tsumaki et al. (1996) J. Cell Biol. 134:1573-82 (characterizing the mouse *collagen type XI* promoter); Deak et al. (1999) Cytogenet. Cell Genet. 87:75-79 (characterizing the mouse *link* promoter); Rhodes et al. (1991) Nuc. Acids Res. 19:1933-39 (characterizing the rat *link* promoter); Issack et al. (2000) J. Orthop. Res. 18:345-50 (characterizing the mouse *COMP* promoter); and Kanai and Koopman (1999) Hum. Mol. Genet. 8:691-6 (characterizing the mouse *Sox9* promoter).

chondrocyte-specific promoters do not exist. The Examiner has not cited any publications or patents that suggest that other chondrocyte-specific promoters do not exist, or any publications or patents that suggest that type II collagen is believed to be the only gene with a chondrocyte-specific promoter. Further, it does not appear that the Examiner has searched for an art-established definition of "chondrocyte-specific." Therefore, the Examiner has not explained why the Examiner doubts the accuracy of Applicants' statements as required by MPEP §2164.04. (See also *In re Marzocchi*, 439 F.2d 220 (C.C.P.A. 1971)). Rather, the Examiner attempts to prematurely shift this burden to Applicants by forcing them to show that chondrocyte-specific promoters do exist (and, further, exist within the Examiner's narrow definition), but this is not the legal standard. (Id.).[9]

In order to satisfy the enablement requirement of 35 U.S.C. §112, an applicant must provide sufficient information so one skilled in the art can make and use the subject of the claims without undue experimentation. Because numerous "chondrocyte-specific promoters" are and were well known in the art at the time of filing (see, e.g., Tab 2 of the Second Neuhold Declaration, The Third Neuhold Declaration, and the Second Askew Declaration), one skilled in the art could simply isolate (or even construct) one of these promoters (e.g., the promoters for

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[9]In addition, the Examiner's statement that "the [Second Neuhold] declaration does not discuss how the CD-RAP/MIA promoter" meets the Examiner's definition of "chondrocyte-specific" (Office Action, dated November 7, 2005 at p. 7), suggests that the Examiner has not fully considered Applicants' rebuttal evidence, i.e., Dr. Neuhold's statements in the Second Neuhold Declaration that *CD-RAP* is coexpressed with *type II collagen*, and that the *CD-RAP* promoter may be used to produce a transgenic mouse according to the pending claims (Memo attached at Tab 2 of the Second Neuhold Declaration). It also suggests that the Examiner did not consider the references cited in the Second Neuhold Declaration to support Dr. Neuhold's factual assertions (Memo attached at Tab 2 of the Second Neuhold Declaration), and that the Examiner did not "weigh all the evidence before him or her, including the specification and any new evidence supplied by the applicant ... and decide whether the claimed invention is enabled." (MPEP §2164.05).

*CD-RAP, aggrecan, link, type IX collagen*, etc.), and follow the examples in the specification to produce a transgenic animal for selective expression of MDEs in joints. Applicants believe that the art-established phrase "chondrocyte-specific" indicates numerous promoter species within the "chondrocyte-specific" genus used in Applicants' instant claims, and therefore submit that the scope of the invention as claimed is enabled. In addition, because Applicants have provided evidence in the above section (in the form of scientific publications, the Second Neuhold Declaration, the Third Neuhold Declaration, and the Second Askew Declaration) showing that chondrocyte-specific promoters have been isolated by others, the Examiner's concern that "no amount of experimentation would ensure that such a promoter existed" has been answered. (Office Action, dated November 7, 2005, at page 12).

For the reasons set forth above, Applicants believe that they have fully enabled a transgenic animal comprised of, *inter alia*, a "chondrocyte-specific promoter," and that the enablement-based rejections of claims 55-57, 59-64, 66-68, 72-77, 79 and 81-100 have been fully answered and successfully overcome. For this reason, Applicants respectfully request withdrawal of these rejections of claims 55-57, 59-64, 66-68, 72-77, 79 and 81-100.

Claim Objections

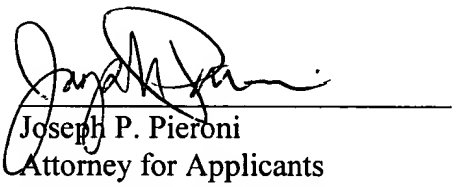
The Examiner has objected to claims 65 and 80 as being dependent upon a rejected base claim. (Office Action, dated November 7, 2005, at page 14). For the reasons set forth above, Applicants believe that all claim rejections have been overcome, and therefore respectfully request withdrawal of the objections to claims 65 and 80.

## CONCLUSION

In light of the above amendments, observations and remarks, Applicants respectfully submit that the presently claimed invention satisfies 35 U.S.C. §112, and is neither disclosed nor suggested by any art of record. Accordingly, reconsideration and allowance of all claims in this application is earnestly solicited.

Applicants' undersigned attorney may be reached in our New York office by telephone at (212) 218-2100. All correspondence should continue to be directed to our below-listed address.

Respectfully submitted,



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